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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,772	09/28/2004	Bryan Glenn Johnson	X-15407	2158

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EXAMINER	
JARRELL, NOBLE E	
ART UNIT	**PAPER NUMBER**
1609	

NOTIFICATION DATE	DELIVERY MODE
06/29/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,772	JOHNSON ET AL.	
	Examiner	Art Unit	
	Noble Jarrell	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *3-10 and 13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,12 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group III in the reply filed on 5/25/2007 is acknowledged. The traversal is on the ground(s) that the examiner has failed to appreciate the single general inventive concept presented in the claims. This is not found persuasive because after analysis of the claims, the invention seems to be a composition comprising distinct antipsychotic agents and a second component, which is any mGlu2/3 receptor agonist regardless of structural makeup. Applicants also traverse the restriction on the grounds that the combinations are not distinct. After analysis, groups I and III are distinct because the specific antipsychotic component is different. In group I, it is clozapine, and in group III, it is olanzapine. Thus, claims 1-2, 11-12, and 19-22 are being examined in the current office action. Claim 2 was inadvertently not included in the original groups I and III.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-2, 11-12, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowley et al. (*Journal of Medicinal Chemistry*, **2001**, *44 (4)*, 477-501, ref CA of 9/28/2004 IDS) and Aghajanian et al. (*Neuropsychopharmacology*, **1999**, *21 (56)*, S122-S133, ref CB of 9/28/2004 IDS).

Rowley et al. teach the use of olanzapine (page 479, column 1, compound 10) as an atypical antipsychotic drug for treating schizophrenia. Rowley teaches that olanzapine is part of a class of antipsychotics in which the 5-HT_2/D_2 ratio is more important than the absolute affinity for each receptor individually. An antipsychotic drug can be considered "atypical" if extrapyramidal side effects (EPS) are reduced and/or they have an enhanced spectrum of antipsychotic efficacy (Aghajanian et al., page S122, paragraph 2-S123, paragraph 1, lines 1-2). Rowley et al. do not teach combination of olanzapine with other active ingredients.

Aghajanian et al. teach the use of group II/III metabotropic glutamate agonists that suppress the 5-HT-induced release of glutamate and thus are therapeutic targets for the treatment of schizophrenia. Aghajanian et al. specifically discuss LY 354740. They do not teach combination of LY 354740 with other active ingredients.

In re Kerkhoven (205 USPQ 1069) supports this 103 rejection. *Kerkhoven* dealt with the production of particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials. The ruling in the case concerning patentability was "it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form third composition that is to be used for very same purpose." In the case of the instant claims, each compound is a known antipsychotic agent, and it is a case of prima facie obvious to combine the components together to form a composition for an identical purpose. Thus, it is obvious to combine two antipsychotic compounds together.

The examiner has noted the comparative data in the specification (figures 5 and 6). Figures 5 and 6 are noted for the synergy shown between olanzapine and the different isomers of the elected compound.

In figure 5, the ambulations of phencyclidine (PCP) fed rats are decreased by ~2000 using the combination of olanzapine and the elected compound, compared to the number of ambulations under olanzapine alone (3000). In figure 6, the number of ambulations for olanzapine (600) was decreased to 400 ambulations when the rats were treated with the combination of olanzapine and the elected compound. Thus, the synergy between olanzapine and the isomers of the elected compound is observed. However, claims 11-12 directed to the components tested are not limited to the treatment of schizophrenia nor are the claims limited to "synergistic" amounts. Thus, the comparative data in the specification is not commensurate with the claims' scope directed to specific components, much less the broader scope covered by claims 1-2 and 19-22.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2 and 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The issue concerning the meaning of "mGlu2/3 agonist" is discussed in the 35 U.S.C. 112, paragraph 2 rejection. Claims 1-2 and 19-22 do not contain generic formulae indicating structural makeup for both active ingredients comprising applicants' invention.

According to the MPEP §2163 I. A. "the issue of a lack of adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. The claimed invention as a whole may not be adequately described if the claims

require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art." The MPEP states in §2163 II 3 ii) "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406."

According to the MPEP §2163.02 Standard for Determining Compliance With the Written Description Requirement, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter". Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))."

This case was filed before Applicants had a clear idea of the structures encompassing the scope of claims 1-2 and 19-22, other than the specific compounds recited in claims 11 and 12.

The specification provides broad areas of future research and speculation, inviting undue experimentation in learning how to use Applicants' invention.

Applicants are reminded of what the U.S. Court of Appeals Federal Circuit wrote in University of California v. Eli Lilly and Co. 43 USPQ2d 1398, "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus." "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). "It is only a definition of a useful result rather than a definition of what achieves that result." "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")".

7. Claims 2, 12, 20, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of schizophrenia, does not reasonably provide enablement for treatment of all psychiatric disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many psychiatric disorders, including schizophrenia, delusional disorder, severe mood disorders, delirium, and dementia (Lake et al. *Drugs and Aging*, **1997**, *11(3)*, 170-177). Applicants also list other psychotic conditions (page 16, lines 15-22), including acute mania. There is no guarantee that

the prepared compositions will effectively treat the disorders that are linked with PCP administration. It is known in the art (Steinpres, R.E. *Behavioural Brain Research*, **1996**, *74*, 45-53, page 45, column 1) that PCP-induced problems are a reliable model for treating schizophrenia.

In addition, the dosage regimens for the scope claimed (an atypical antipsychotic and an mGlu2/3 agonist) are not set forth for a single use, much less claimed for all uses. The only guidance for dosage is described in figures 1-8.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to compositions comprising an antipsychotic agent and an mGlu2/3 receptor agonist. Thus, the claims taken together with the specification imply that the mGlu2/3 agonist improves the ability of olanzapine to reduce PCP-induced ambulations, and consequently, schizophrenia, in rats.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

There is no prior art of record with the claimed composition having the two components. However, the examiner is only aware that olanzapine is effective against schizophrenia.

As far as the examiner understands, mGlu2/3 agonists are only effective as anti-schizophrenic drugs.

(5) The relative skill of those in the art:

One of ordinary skill in the art is knowledgeable about the different effects of PCP on the behavior of animals.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for the synergistic combination of olanzapine with the specified second active ingredients in claims 11, 13, 15, and 17.

However, the specification does not provide guidance for all combinations of an antipsychotic agent and an mGlu2/3 receptor agonist.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the limited scope of the invention and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-2 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply.

1. The scope of "mGlu 2/3 receptor agonist" is unclear for several reasons. First, there is no guidance to the structure of the agonist. Second, there is no guidance as to what constitutes an effective mGlu2/3 receptor agonist. What minimum IC_{50} value is necessary for a compound to be considered such an agonist? Third, the designation 2/3 is not clear since it could be interpreted or requiring activity at both the 2 and 3 or 2 or 3. Extensive testing would be required to determine what is and what is not within the intended scope.

2. What constitutes an "atypical antipsychotic"? While it is known that atypical antipsychotics have a lower tendency for extrapyramidal side effects, it is not clear how they achieve minimization of such side effect or how they treat certain symptoms of schizophrenia. Note Kapur (provided by the examiner) discusses many possible mechanisms of action other than the D_2 receptor blockade which may contribute to their beneficial effects. See section entitled "Atypical antipsychotic: What is atypical about their molecular pharmacology?" on page 874. In the absence of any guidelines in the specification as to what binding affinity for a particular receptor is needed to qualify, much less selectivity ratio between such receptor and the D_2 receptor, it cannot be readily determined what is and what is not within the instant scope.

10. Claims 2, 12, 20 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants claim to treat subjects "susceptible to a psychiatric disorder." The problem with this phrase renders the intended host unclear. Also, people may be susceptible to psychiatric disorders, whether they may know it or not. Risk factors for psychotic disorders include genetic predisposition, sensory impairment, cerebral atrophy and brain injury, general physical illness, neurochemical changes common in aging, certain premorbid personalties, gender, and social factors (see Lake et al. *Drugs and Aging*, **1997**, *11(3)*, 170-177).

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on Monday-Friday from 7:30 to 6:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NJ

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